the dose is 5 mg total anti-Tac if said patient has sIL-2R levels of 2,000 - 10,000 units/ml, the dose is 10 mg of total anti-Tac if the patient has sIL-2R levels of 10,000 - 50,000 units/ml, and the dose is 20 mg of total anti-Tac if said patient has sIL-2R levels of greater [that] than 50,000 units/ml; and

b) administering said dosage to said patient to eliminate disease-associated Tac-positive cells.

REMARKS

Applicant respectfully requests favorable reconsideration in view of the herewith presented amendment and remarks. Claim 27 is pending in the instant application.

Response to Section 112 Rejection

Claim 27 has been rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the claimed methods as predetermining the three dosage/amount/soluble level determinations set forth in the claimed methods prior to administering ^{90}Y-conjugated anti-Tac as it reads on treating leukemia/lymphoma as a disease associated with elevated levels of Tac-positive cells, does not provide enablement for methods of treating patients with any disease associated with elevated levels of Tac positive cells. Applicants respectfully disagree with this rejection.

The claimed invention relates to a method of determining an appropriate dose of ^{90}Y-conjugated Tac-antibody in patients suffering from diseases associated with elevated levels of Tac-positive cells. Applicants specification teaches that malignancy, autoimmune disorders,

and allograft rejection are pathological states that are related to elevated levels of Tac-positive cells and with elevated levels of soluble IL-2R. The claim directly correlates the appropriate dosage of ^{90}Y-conjugated Tac-antibody with the specific level of soluble IL-2R and teach one of skill in the art how to reduce levels of Tac-positive cells. Thus, an appropriate dosage determination can be made for any such disease having soluble IL-2R levels within the claimed ranges. Because dosage is directly related to the levels of soluble IL-2R, one skilled in the art can readily recognize the appropriate dose for a patient having any disease associated with elevated levels of anti-Tac based upon the soluble IL-2R levels. This test, which is fully disclosed in the instant specification, is the basis of the claimed invention and does not entail undue experimentation. Moreover, applicants have amended claim 27 to remove a direct reference to the word "disease." Reconsideration and withdrawal of this §112 rejection is respectfully requested.

Response to Section 102(b) Rejection

Claim 27 has been rejected under 35 U.S.C. §102(b) as being anticipated by or in the alternative, under 35 U.S.C. §103 as obvious over Waldmann (*Blood* 82: 1701-1712, 1993), as evidenced by Waldmann et al. (*Blood* 86: 4063-4075, 1995) and/or Vriesendorp et al (*Int. J. Radiation Oncology* 22:37-45, 1991). The Examiner asserts that the evidentiary references are provided to support the Examiner's position that the prior art teaching of 5-15 mCi doses of ^{90}Y anti-Tac *inherently* encompasses the total amount of 2-20 mg anti-Tac encompassed by the claimed methods. Applicants respectfully disagree with this rejection.

The 1993 Waldmann article describes the use of *unlabelled* anti-Tac in patients with ATL. These patients are described to have a "pretherapy serum soluble IL-2R (sIL-2Rα)

levels of 920 to 230,370 U/mL". (see page 1703, col. 2, lines 7-8 of "Results" section). The "initial basic protocol" as described in column 2 on page 1704, states that the anti-Tac therapy "involved the administration of 20 mg anti-Tac on two occasions during the first week and 40 mg anti-Tac on two occasions during the second week of therapy for each patient (Table 2)". Based upon the results of these initial treatment protocols the dosages were altered, which is described on page 1705, column 2. Here, Waldmann states:

> In light of these early observations, to achieve a rapid saturation of IL-2R, the basic dosing schedule was altered for the final 10 patients in the group so that 50 mg anti-Tac per patient was administered on two occasions during the first week of therapy and on two occasions during the second week of therapy.

Thus, the Waldmann article teaches that it is preferred to use a 50 mg anti-Tac dose, in order to saturate IL-2R.

It appears the Examiner has focused his attention on a single paragraph in the Waldmann reference (page 1711, first full paragraph) which indicates that the authors "initiated a dose-escalation trial with ^{90}Y-labeled anti-Tac for the treatment of ATL." The passage also states: "At the 5- to 15-mCi doses used, 10-15 patients underwent a partial (eight patients) or complete (two patients) remission following ^{90}Y anti-Tac therapy." These statements are the entirety of the disclosure relied upon by the Examiner as anticipating and/or obviating the claim.

Vriesendorp describes the use of radiolabeled antiferritin antibodies for radioimmunoglobulin therapy for refractory Hodgkin's disease patients. Vriesendorp describes three different labeling procedures for chelating indium and yttrium. The first method uses isothiocyanoto-benzyl DTPA (diethylene triamine pentaacetic acid) or "ITCB method" developed by Hybritech, Inc. The second method employs a diester linkage ethylene glycol bis (succinimethyl succinate) was introduced between the antibody and the chelator which is

referred to at the "EGS method." The third method is site specific conjugation to the antibody oligosaccharide moiety as described in reference 16 of Vriesendorp. These conjugation methods produced antibodies with specific activities of "2-5 mCi per mg protein for indium-111 labeled antibodies, and between 5-40 mCi per mg protein for yttrium-90 labeled antibodies." Vriesendorp does not indicate which of the methods were used to chelate yttrium, nor is there any indication as to why there is such a broad range of radioactivity per mg of antibody.

The present invention does not use an antiferritin antibody, nor does it necessarily use the same method of yttrium conjugation described by Vriesendorp. Thus, it is not possible to extrapolate from Vriesendorp to determine the radioactivity per mg of antibody in Waldmann. One skilled in the art recognizes that specific activity is not a universally applicable number arrived at by correlation to other antibodies conjugated to radionucleides by other methods. One skilled in the art would not read Vriesendorp which labeled antiferritin antibodies with yttrium-90, and conclude that anti-Tac labeled with yttrium-90, (or any other antibody labeled with yttrium-90) regardless of the method of conjugation, must have the same specific activity. In fact, the instant specification makes clear that the concentration of labeled Tac antibody administered to a patient is carefully controlled by diluting the labeled antibody with unlabeled antibody to control the total quantity of antibody administered. *See* page 42, lines 14-18.

The combination of Waldmann in view of Vriesendorp does not teach or suggest the use of yttrium-90 conjugated anti-Tac in any dosage within the ranges claimed for a given level of soluble IL-2R. Vriesendorp does not provide the missing teaching that 2-20 mg of anti-Tac should be used. One skilled in the art would not conclude from the Waldmann 1993 and Vriesendorp references that 5-15 mCi of yttrium-90 conjugated to 2-20 mg anti-Tac should be administered to patients with any particular soluble IL-2R level. There is no correlation between

the labeling of yttrium-90 to a antiferritin antibody to yttrium-90 labeling of a Tac antibody. Thus, this combination of prior art does not render obvious claim 27.

The Examiner repeatedly points out that "for examination purposes given the claimed recitation; all that is required of the prior art is to provide a dosage of mCi and an amount of ^{90}Y-conjugated anti-Tac to a patient with one of the soluble IL-2R levels." *See, e.g.* page 4, 6th paragraph, and page 7, first paragraph of Paper No. 29. Applicants respectfully disagree with this position. However, *assuming arguendo* this position is appropriate, the Examiner has not pointed to a single such scenario in the cited art, that is, the cited prior art does not show 2-20 mg of anti-Tac conjugated to 5-15 mCi ^{90}Y being administered to a patient with one of the soluble IL-2R levels claimed. Thus, the Examiner has not made a prima facie showing of anticipation and/or obviousness against claim 27.

Waldmann et al (1995) has been cited by the Examiner as "disclos[ing] that the Phase I trials disclosed in the Waldmann, *Blood*, 1993 teaching led to algorithm encompassed by the claimed methods." (*See* page 4, first paragraph of Paper No. 29). The Examiner concludes: "[t]herefore, given that the algorithm relied upon these Phase I studies; it would be inherent that the dosing set forth in the Phase I studies would meet the claimed dosage/amount/soluble level determination." This argument is seriously flawed.

As an initial matter, Waldmann et al (1995) is not prior art to the instant application. This reference was published on December 1, 1995, whereas the instant application was filed on June 7, 1995. Thus, the reference was published after the effective filing date of the instant application, and therefore cannot constitute prior art pursuant to sections 102 or 103 of the Patent Statute.

Nothing in the Waldmann 1993 reference teaches or suggests the dosing determination as claimed. Instead, the reference describes the use of a different dosage, i.e. 20-50 mg of anti-Tac for the treatment of patients. The position that the naked description of a study using 5-15mCi of ^{90}Y conjugated anti-Tac *inherently* discloses the dosage determination claimed is incorrect. Nothing in the references teaches or suggests the use of anti-Tac at doses less than the 20-50 mg described in the article. In fact, the article suggests that the 50 mg dose is preferred. There is simply no teaching or suggestion to the skilled artisan that (a) the dose should be less than 20 mg (i.e. 2-20 mg, as claimed), or (b) that there is any correlation between the soluble IL-2R levels and the recommended dosage.

The doctrine of inherency is misplaced based upon the present facts. On the one hand, the Examiner argues that the invention is obvious in view of Waldmann (1993), as evidenced by Waldmann (1995) and/or Vriesendorp. Obviousness cannot be predicated upon inherency. *In re Rijckaert*, 28 USPQ.2d 1955, 1957 (Fed. Cir. 1993). Obviousness requires some explicit or implicit teaching or suggestion in the prior art of the invention as a whole. The Examiner has taken a "retrospective view" of the art, that is, the Examiner has applied a reference, published *after* the filing date of the instant application, to teach that which is missing from the prior art. This is a classic case of the improper use of hindsight to reach the instant invention. The Federal Circuit has repeatedly pointed out the improperness of such action. For example, in *In re Newell*, (891 F.2d 899, 901 (Fed. Cir. 1989)), the court stated:

> A retrospective view of inherency is not a substitute for some teaching or suggestion which supports the selection and use of the various elements of the particular claimed combination. It is well established that in deciding that a novel combination would have been obvious, there must be supporting teaching in the prior art. 'That which may be inherent is not necessarily known. Obviousness cannot be predicated on what is unknown.'
> (citations omitted.)

Furthermore, there is nothing in the Waldmann reference taken alone or in view of Vriesendorp that would lead the skilled artisan to select a yttrium-90 anti-Tac at the dosage ranges claimed for patients having a given soluble IL-2R level. There is no basis in Waldmann 1993, taken alone or in combination with Vriesendorp that would lead the skilled artisan to a reasonable expectation of success. The Examiner's view that success would be inherent is flawed. To preclude patentability under 35 U.S.C. §103, there must be some predictability of success in any attempt to combine elements of reference processes. The view that success would have been "inherent" cannot substitute for a showing of reasonable expectation of success. *In re Rinehart*, 531 F.2d 1048, 1054 (C.C.P.A. 1976).

In the alternative, the Examiner asserts that the claim is anticipated by Waldmann 1993, based upon the inherent disclosure of the claimed method. The reference itself does not teach or suggest the claimed method. In fact, as discussed above, the reference specifically teaches the use of unlabeled anti-Tac at doses of 20-50 mg, preferably at the higher dose. In one paragraph, the authors provide a cursory description of a study using yttrium-90 labeled anti-Tac. There is no teaching or suggestion as to the amount of anti-Tac provided to patients, nor is there any teaching or suggestion that the amount of the conjugate administered is related to the soluble levels of IL-2R. As the Examiner is well-aware, an anticipatory reference must teach every element of a claim, either expressly or under the doctrine of inherency. However, as stated by the Federal Circuit in *Continental Can Co. USA, Inc. v. Monsanto Co.* (948 F.2d 1264, 1268 (Fed. Cir. 1991)),

> [t]o serve as an anticipation when the reference is silent about the asserted inherent characteristic, such gap in the reference may be filled with recourse to extrinsic evidence. Such evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, *and that it would be*

> *so recognized by persons of ordinary skill.* ... [Thus], this modest flexibility in the rule that 'anticipation' requires that every element of the claims appear in a single reference accommodates situations where the common knowledge of technologists is not recorded in the reference; that is, *where the technological facts are known to those in the field of the invention, albeit not known to judges.*

Therefore, it is the Federal Circuit's position that for a teaching to be disclosed under the doctrine of inherency, the missing matter must be "recognized by persons of ordinary skill". In stark contrast, the claimed method is not only NOT taught or suggested by Waldmann 1993, but one skilled in the art would not have known how to determine the dosages of yttrium-90 conjugated anti-Tac based upon this reference, or any prior art reference cited by the Examiner. Thus, Waldmann does not teach expressly, or under the doctrine of inherency, the claimed method. Applicants respectfully request reconsideration and withdrawal of this rejection.

Response to Section 102(f) Rejection

Claim 27 stands rejected under 35 U.S.C. §102(f) because the Examiner contends that the applicant did not invent the claimed subject matter. In particular, the Examiner refers to Waldmann et al. (1995) *Blood* 86:4063 as presenting "an ambiguity with regard to inventorship." Applicant respectfully disagrees with this ground of rejection.

A scientific publication is not a legal document. The requirements for being a co-author do not correspond to the legal requirements for being an inventor. The statement on page 4064, column 2 referred to by the Examiner merely indicates which of the several co-authors assisted in the development of the algorithm. It is not a legal analysis of inventorship as the Examiner mistakenly believes.

> As an initial matter, we hold that authorship of an article by itself does not raise a presumption of inventorship with respect to the

> subject matter disclosed in the article. Thus, coauthors may not be presumed to be coinventors merely from the fact of coauthorship.

In re Katz, 687 F.2d 450, 455.

The Examiner contends that "it is incumbent on applicant to provide a satisfactory showing which would lead to a reasonable conclusion that applicant alone is the inventor of the claimed invention." Applicants assert that the required showing of sole inventorship has been established in this case and no reasonable cause for additional proof of sole inventorship has been made of record in this case. The Examiner is directed to the declaration of Dr. Waldmann dated September 13, 1995 wherein Dr. Waldmann states "I made and conceived this invention . . . ." The Examiner's is also directed to the declaration and power of attorney dated September 13, 1995 wherein Dr. Waldmann states "I believe I am the original, first and sole inventor of the subject matter claimed . . . ." Further, the Examiner's attention is directed to the declaration of Dr. Waldmann dated March 22, 1999 is which Dr. Waldmann states "I am the inventor of the subject matter claimed . . . ." The cited Waldmann article does not create ambiguity concerning the inventorship of the present claim.

> Turning to the rejection of the claims under 35 U.S.C. 102(f) on the basis that the Kusco publication offers sufficient evidence that appellant himself did not invent the subject matter claimed herein, and that the declarations of record fail to adequately rebut such evidence, we will not sustain the rejection. Where an applicant by oath or declaration states that he is the sole inventor of a particular invention, strong evidence is required to reach a contrary conclusion. A publication, particularly one dated more than a year after appellant's filing date, which merely lists as literary co-authors, three individuals in addition to appellant is not, in our view, strong evidence indicating that appellant is not a sole inventor of the subject matter claimed herein. We recognize that Section 102(f) does not expressly include a reference to dates of invention or relative timing of the events presented by the evidence. Nevertheless it is clear that most, if not all, determinations under Section 102(f) involve the question of whether one party derived an invention from another, and the

> relative dates of the events in evidence are important and are considered in deciding such issues.

Ex parte Kusko, 215 USPQ 972.

Applicants respectfully assert that the Waldmann article, published about 6 months after the filing date of the present application is not the required "strong evidence indicating that appellant is not a sole inventor of the subject matter claimed herein" required for a showing of ambiguity concerning inventorship. Therefore, applicants respectfully request reconsideration and withdrawal of this ground of rejection.

Response to Section 103(a) Rejection

Claims 27 stands rejected under 35 U.S.C. § 103(a) as being unpatentable over Waldmann (1993) *Blood* 82:1701-1712 and/or Waldmann et al. (1994) *Important Adv. Oncol.* and/or Waldmann (1993) *Leukemia* 7, Suppl. 2:S151-S156 and/or Waldmann (1994) *Annl. Oncol.* 5:13-17 in view of Vriesendorp et al. (1991) *Int. J. Radiation Oncology* 22:37-45 and Rubin et al. (1990) *Ann. Int. Med.* 113:619. In particular, the Examiner contends that the four Waldmann articles describe administration of 5 - 15 mCi doses of ^{90}Y anti-Tac antibody to patients. Vrisendorp allegedly describes that the specific activity for yttrium-90 labeled antibodies is 5 - 50 mCi per mg protein. Rubin allegedly describes that soluble IL-2 receptors are measured in a number of human diseases. Applicants respectfully disagree with this rejection.

As describe above and conceded to by the Examiner, the Waldmann articles simply mention 5-15 mCi doses of ^{90}Y-labeled anti-Tac antibodies. There is no suggestion of the amount in mg of antibody the radiation dosage is contained in, nor is there any suggestion of the sIL-2 levels of the patients. More importantly, there is no suggestion of a relationship between

the radiation dosage, the amount of antibody in mg, and the level of sIL-2. Combining Vriesendorp and Rubin to the Waldmann articles does not cure the deficiencies of the Waldmann articles.

Vriesendorp describes the use of radiolabeled antiferritin antibodies for radioimmunoglobulin therapy for refractory Hodgkin's disease patients. Vriesendorp describes three different labeling procedures for chelating indium and yttrium. The first method uses isothiocyanoto-benzyl DTPA (diethylene triamine pentaacetic acid) or "ITCB method" developed by Hybritech, Inc. The second method employs a diester linkage ethylene glycol bis (succinimethyl succinate) was introduced between the antibody and the chelator which is referred to at the "EGS method." The third method is site specific conjugation to the antibody oligosaccharide moiety as described in reference 16 of Vriesendorp. These conjugation methods produced antibodies with specific activities of "2-5 mCi per mg protein for indium-111 labeled antibodies, and between 5-40 mCi per mg protein for yttrium-90 labeled antibodies." Vriesendorp does not indicate which of the methods were used to chelate yttrium, nor is there any indication as to why there is such a broad range of radioactivity per mg of antibody.

The present invention does not use an antiferritin antibody, nor does it necessarily use the same method of yttrium conjugation described by Vriesendorp. Thus, it is not possible to extrapolate from Vriesendorp to determine the radioactivity per mg of antibody in Waldmann. One skilled in the art recognizes that specific activity is not a universally applicable number arrived at by correlation to other antibodies conjugated to radionucleides by other methods. One skilled in the art would not read Vriesendorp which labeled antiferritin antibodies with yttrium-90, and conclude that anti-Tac labeled with yttrium-90, (or any other antibody labeled with yttrium-90) regardless of the method of conjugation, must have the same specific activity. In

fact, the instant specification makes clear that the concentration of labeled Tac antibody administered to a patient is carefully controlled by diluting the labeled antibody with unlabeled antibody to control the total quantity of antibody administered. *See* page 42, lines 14-18.

According to the Examiner, Rubin merely "reviews that soluble IL-2 receptors were measured in a number of human diseases, including malignancies encompassed by the claimed invention."

The combination of the Waldmann articles in view of Vriesendorp and Rubin does not teach or suggest the use of yttrium-90 conjugated anti-Tac in any dosage within the ranges claimed for a given level of soluble IL-2R. Neither Vriesendorp nor Rubin provide the missing teaching that 2-20 mg of anti-Tac should be used. One skilled in the art would not conclude from the Waldmann articles, Vriesendorp and Rubin that 5-15 mCi of yttrium-90 conjugated to 2-20 mg anti-Tac should be administered to patients with any particular soluble IL-2R level. There is no correlation between the labeling of yttrium-90 to a antiferritin antibody to yttrium-90 labeling of a Tac antibody to soluble IL-2 receptor levels. Thus, this combination of prior art does not render obvious claim 27.

No additional fee is believed to be necessary.

The Commissioner is hereby authorized to charge any additional fees which may be required for this response, or credit any overpayment to Deposit Account No. 13-4500, Order No. 2026-4003US3.

In the event that an extension of time is required, or which may be required in addition to that requested in a petition and for an extension of time, the Commissioner is requested to grant a petition for that extension of time which is required to make this response timely and is hereby authorized to charge any fee for such an extension of time or credit any

overpayment for an extension of time to Deposit Account No. 13-4500, Order No. 2026-4003US3. A DUPLICATE COPY OF THIS SHEET IS ATTACHED.

Respectfully submitted,

MORGAN & FINNEGAN, L.L.P.

Dated: September 12, 2000

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